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# Lifestyle intervention in gastroesophageal reflux disease

Ness-Jensen, Eivind; Hveem, Kristian; El-Serag, Hashem B; Lagergren, Jesper

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## **TITLE PAGE**

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**Authors:** Eivind Ness-Jensen, M.D., Ph.D.<sup>1,2</sup>; Kristian Hveem, M.D., Ph.D.<sup>2</sup>; Hashem El-Serag, M.D., M.P.H.<sup>1,3</sup>; and Jesper Lagergren, M.D., Ph.D.<sup>1,4</sup>

<sup>1</sup>Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

<sup>2</sup>HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, Levanger, Norway

<sup>3</sup>Section of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, Texas, USA

<sup>4</sup>Section of Gastrointestinal Cancer, Division of Cancer Studies, King's College London, United Kingdom

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**Abbreviations (alphabetically):** ACG – American College of Gastroenterology

AGA – American Gastroenterological Association

BMI – body mass index

CAG – Canadian Association of Gastroenterology

CI – confidence interval

GERD – gastroesophageal reflux disease

HUNT – The Nord-Trøndelag health study

OR – odds ratio

PPI – proton pump inhibitor

RCT – randomized clinical trial

**Corresponding author:** Eivind Ness-Jensen, M.D., Ph.D.

Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery, Karolinska

Institutet, NS 67, 171 76 Stockholm, Sweden

E-mail: eivind.ness-jensen@ki.se

Telephone: 0047 918 60 549

Fax number: 0046 8 51776280

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**ABSTRACT (word count 248, maximum 260 words)**

**Background & Aims** Gastroesophageal reflux disease (GERD) affects up to 30% of adults in Western populations and is increasing in prevalence. GERD is associated with lifestyle factors, particularly obesity and tobacco smoking, and carries a risk of several adverse outcomes, including esophageal adenocarcinoma. The aim of this systematic review was to assess the role of lifestyle intervention in the treatment of GERD.

**Methods** Literature searches were performed in PubMed (from 1946), EMBASE (from 1980), and the Cochrane Library (no start date) to October 1, 2014. Meta-analyses, systematic reviews, randomized clinical trials (RCTs) and prospective observational studies were included.

**Results** Weight loss was followed by decreased time with esophageal acid exposure in two RCTs (from 5.6% to 3.7% and from 8.0% to 5.5%, respectively), and reduced reflux symptoms in prospective observational studies. Tobacco smoking cessation reduced reflux symptoms in normal weight individuals in a large prospective cohort study (odds ratio 5.67). In RCTs, late evening meals increased time with supine acid exposure compared to early meals (5.2% points change), and head of the bed elevation decreased time with supine acid exposure compared to a flat position (from 21% to 15%). In a placebo-controlled RCT, high dietary fiber intake decreased heartburn.

**Conclusions** Weight loss and tobacco smoking cessation should be recommended to GERD patients who are obese and smoke, respectively. Avoiding late evening meals and head of the bed elevation is effective in nocturnal GERD and high dietary fiber intake might reduce heartburn.

**Keywords:** GERD; heartburn; acid regurgitation; therapy; treatment

**MAIN TEXT (word count 3,398, maximum 6,000 words, including figure and table legends, and references)**

Gastroesophageal reflux disease (GERD), defined by at least weekly symptoms of heartburn or acid regurgitation, is increasingly common.<sup>1</sup> The prevalence in adults ranges from 30% in some Western populations to below 10% in East Asian populations, and the incidence is about 5/1000 person-years in Western populations.<sup>1</sup> GERD is associated with reduced health-related quality of life,<sup>2</sup> decreased work productivity<sup>3</sup> and increased risk of esophageal adenocarcinoma.<sup>4</sup> The annual incidence of esophageal adenocarcinoma is increasing worldwide, from 3.5% in Scotland to 8.1% in Hawaii, which parallels the increasing prevalence of GERD.<sup>5</sup> In addition, GERD diagnostic tests and treatments carry high societal costs.<sup>6</sup>

The pathophysiology of GERD is dominated by functional and anatomic defects at the gastroesophageal junction, including reduced pressure and increased reflux episodes associated with transient relaxations of the lower esophageal sphincter and formation of hiatal hernia which promotes and facilitates reflux.<sup>7-9</sup> Esophageal motility and salivary bicarbonate contribute to esophageal acid clearance and buffering, respectively, and reduce acid contact time in the esophagus.<sup>10,11</sup> Visceral obesity increases the pressure over the gastroesophageal junction, thus facilitating reflux,<sup>12</sup> while tobacco smoking reduces the lower esophageal sphincter pressure and salivary bicarbonate secretion, which facilitates reflux and decreases acid buffering, respectively.<sup>13,14</sup>

The main established risk factors of GERD are heredity, obesity and tobacco smoking.<sup>15-18</sup> High dietary fiber intake and moderate physical exercise seem to reduce this risk,<sup>18</sup> while sex and age do not strongly influence the risk of GERD.<sup>19,20</sup> Obesity is of particular interest since it is increasing in prevalence in parallel with GERD, and several studies have shown an increased risk of GERD and esophagitis with obesity, especially abdominal obesity.<sup>21,22</sup>

GERD is typically diagnosed by the cardinal symptoms heartburn or acid regurgitation<sup>23</sup> and symptom resolution following acid-inhibition with a proton pump inhibitor (PPI).<sup>24,25</sup> If symptoms do not

resolve, endoscopy is usually performed and mucosal erosions (esophagitis) or peptic strictures are diagnostic of GERD.<sup>26</sup> Endoscopy can also reveal Barrett's esophagus, a premalignant columnar metaplasia, and esophageal adenocarcinoma. If endoscopy is normal, esophageal pH-measurement can still reveal pathologic acid reflux (pH <4).<sup>27</sup> The pH-measurement can be combined with impedance-measurement to detect reflux of weakly acidic or non-acidic liquid and gas, which can cause reflux symptoms refractory to acid inhibition.<sup>28</sup>

The treatment of GERD is primarily by medication with antacids, H<sub>2</sub>-receptor antagonists and PPIs, while surgery with fundoplication is used in selected patients. Surgery carries a risk of adverse events, including postoperative complaints of dysphagia, flatulence and inability to belch or vomit.<sup>29</sup> Recent evidence also shows that long-term PPI medication is hampered by adverse effects. This includes secondary hypergastrinemia and rebound acid hypersecretion, inducing reflux symptoms at withdrawal of PPI medication;<sup>30</sup> increased risk of enteric infections and community acquired pneumonia, probably due to increased gastric pH causing reduced host defence;<sup>31,32</sup> and increased risk of hip and vertebral fractures, probably due to malabsorption of calcium.<sup>33</sup>

This review addresses lifestyle intervention in the treatment of GERD and compares existing evidence with current guidelines.

## **METHODS**

Systematic literature searches on lifestyle intervention in GERD were performed in MEDLINE using PubMed from 1946 and EMBASE using OvidSP from 1980 to October 1, 2014. In addition, the Cochrane Library was searched, last time October 1, 2014. The searches included thesaurus terms (MeSH in MEDLINE and Emtree in EMBASE): "gastroesophageal reflux", "heartburn", "peptic esophagitis" (EMBASE)/"esophagitis, peptic" (MEDLINE) and "non-erosive reflux disease" (EMBASE). Randomized clinical trials (RCTs), prospective observational studies, and meta-analyses and

systematic reviews of RCTs or observational studies of GERD patients were included. The searches were limited to the English language and research on adult humans. The evidence of interventions was graded using the American Heart Association's guidelines: Multiple populations evaluated, data derived from multiple RCTs or meta-analyses (**Level A**); limited populations evaluated, data derived from a single RCT or non-randomized studies (**Level B**); and very limited populations evaluated, only consensus opinion of experts, case studies or standard of care (**Level C**).

## RESULTS

### Literature searches

Literature searches on lifestyle intervention identified 579 and 453 studies in MEDLINE and EMBASE, respectively, of which 15 met the inclusion criteria (**Figure, Table and eTable**). No Cochrane reviews on lifestyle intervention in GERD were identified. Four management guidelines were assessed: the Canadian Association of Gastroenterology (CAG) consensus (2005);<sup>24</sup> the American College of Gastroenterology (ACG) practice guidelines (2005);<sup>25</sup> the American Gastroenterological Association (AGA) medical position statement and technical review (2008);<sup>34,35</sup> and a more recent guideline by Katz et al. (2013).<sup>36</sup>

### Lifestyle interventions

Lifestyle interventions in GERD have traditionally included avoidance of foods that may precipitate reflux episodes and heartburn (e.g., coffee, alcohol, chocolate, peppermint, citrus, carbonated drinks and spicy foods) and behavioral changes with weight loss, smoking cessation, head of bed elevation, avoiding large meals and avoiding recumbence after meals or meals before bedtime.<sup>34,35</sup> Until recently, these interventions were mainly based on case series.<sup>37</sup> However, new supportive evidence has emerged.



### **Weight loss**

Three RCTs in severely obese individuals compared weight loss by gastric balloon distension with sham treatment combined with dietary guidance, physical exercise and behavioral therapy, and showed reduced esophageal acid exposure with weight loss.<sup>38-40</sup> In the first RCT, including 17 patients, 3 of 5 patients with pathological pH-measurements got normalized pH-measurements with weight loss of 31.3-44.0 kg after 4 months.<sup>38</sup> In the second RCT, 23 patients with a mean weight loss of 11.2 kg within 13 weeks had decreased time with esophageal pH <4 (from 5.60% to 3.72%,  $P < 0.05$ ).<sup>39</sup> Moreover, there was a strong correlation between decreased waist circumference and acidic reflux time ( $r=0.78$ ,  $P=0.000$ ).<sup>39</sup> These results were supported by the third RCT of 17 sham treated patients, where mean weight loss of 12.5 kg within 13 weeks improved time with upright pH <4 (from 8.0% to 5.5%,  $P < 0.05$ ).<sup>40</sup>

A larger RCT compared obese participants randomized to a structured weight loss program ( $n=167$ ) or a telephone-based group conference on weight management ( $n=165$ ). The prevalence of reflux symptoms decreased (from 37% to 15%,  $P < 0.01$ ) and the symptom score improved (Reflux Disease Questionnaire,  $P < 0.01$ ) after 6 months of weight loss (mean body mass index (BMI) decreased from 34.7 to 30.2), irrespective of treatment group.<sup>41</sup>

These results were confirmed in 2 uncontrolled prospective cohort studies of GERD patients.<sup>42,43</sup> A study of 8 extremely obese patients (mean BMI 43.5) showed significant improved total time with pH <4 (from 5.1% to 2.5%,  $P=0.022$ ) and reflux symptoms score (Distress Subscale of Gastroesophageal Reflux Disease Symptom Assessment Scale from 1.28 to 0.72,  $P=0.0004$ ) after 4 days on a very low-carbohydrate diet and a mean weight loss of 1.7 kg.<sup>42</sup> Moreover, a study of 34 patients with mean BMI of only 23.5, reflux symptoms and either normal endoscopy or low grade esophagitis also showed significant correlation between weight loss after dietary advice (mean BMI decrease 1.7) and reflux symptom score (modified DeMeester questionnaire,  $r=0.548$ ,  $P < 0.001$ ).<sup>43</sup>

Two large prospective population-based cohort studies showed that weight reduction dose-dependently decreased reflux symptoms.<sup>44,45</sup> The Nurses' Health Study, an observational cohort study of 10,545 women, showed a dose-dependently reduced risk of reflux symptoms among women who had decrease in BMI compared to women with no BMI change (odds ratio (OR) 0.64, 95% confidence interval (CI) 0.42-0.97 with >3.5 units decrease in BMI, *P* for trend <0.001).<sup>44</sup> The HUNT study, a prospective population-based cohort study of 29,610 participants also showed a dose-dependent association between weight loss and the chance of losing reflux symptoms (OR 2.42, 95% CI 1.88-3.11 with >3.5 units decrease in BMI, *P* for trend <0.001). In this study, decrease in BMI was also associated with an increased chance of losing reflux symptoms with medical treatment (OR 1.98, 95% CI 1.45-2.72 with >3.5 units decrease in BMI and no or less than weekly medication compared to OR 3.96, 95% CI 2.03-7.65 with >3.5 units decrease in BMI and at least weekly medication).<sup>45</sup>

Challenging these results, a small RCT showed that weight loss (mean 10.8 kg) did not have significant effects on symptoms, esophagitis or pH-measurements in obese patients (mean BMI=31.4) with GERD who were randomized to a low-caloric diet (430 kcal/day) for 6 months (n=10) or not (n=9).<sup>46</sup> This might be explained by the inclusion of patients with hiatal hernia, which is not reversible with weight loss. In addition, a prospective population-based cohort study of 637 individuals showed no association between weight loss and reflux symptoms, but since weight loss was self-reported it might be overestimated.<sup>47</sup>

### ***Tobacco smoking cessation***

A prospective population-based cohort study (the HUNT study) of 29,610 participants showed that smoking cessation was associated with decreased severe reflux symptoms in normal weight individuals on medical treatment, compared to participants who continued smoking daily (OR 5.67, 95% CI 1.36-23.64).<sup>48</sup> However, there was no similar association in overweight (BMI 25.0-29.9) or obese (BMI ≥30.0) individuals (OR 1.24, 95% CI 0.57-2.71 and OR 1.29, 95% CI 0.53-3.17,

respectively). A possible explanation for these findings is that GERD pathophysiology in obese individuals is strongly dictated by weight, while smoking plays a minor role, but smoking is a more important factor in non-obese individuals.

### ***Dietary interventions***

A RCT showed no influence of weight loss following a 6 month period of low-caloric diet (430 kcal/day) on GERD.<sup>46</sup> However, a small non-randomized study of 8 severely obese patients (mean BMI=43.5) who lost weight (1.7 kg) on a 4-day very low-carbohydrate diet (<20g/day) showed a decreased total time with pH <4 (from 5.1% to 2.5%,  $P=0.022$ ) and reflux symptoms score (from 1.28 to 0.72,  $P=0.0004$ ).<sup>42</sup>

A crossover RCT of 30 patients randomized to a late meal (2 hours before bedtime) or an early meal (6 hours before bedtime) showed more pH-verified supine reflux after the late evening meal (mean change 5.2%,  $P=0.002$ ).<sup>49</sup>

A RCT that compared patients using a dietary fiber product (n=15) with placebo (n=15) for 2 weeks, showed an increased number of days without heartburn (mean 1.87 and 0.73, respectively,  $P < 0.05$ ) and reduced severity score (mean 7.7 and 13.3, respectively,  $P < 0.05$ ) in the fiber group.<sup>50</sup>

A systematic review based on observational studies showed no evidence of carbonated beverages promoting GERD.<sup>51</sup>

Regarding other potential dietary interventions there were no studies meeting the search criteria.

### ***Head of bed elevation***

A systematic review concluded that head of the bed elevation could reduce GERD,<sup>37</sup> based on one crossover RCT of 15 GERD participants, where elevation of the head of the bed by a 10 inch wedge decreased esophageal pH <4 time compared to a flat position (15% and 21%, respectively,  $P < 0.05$ ).<sup>52</sup>

## DISCUSSION

RCTs have shown reduced reflux symptoms and esophageal acid exposure with weight loss,<sup>38-41</sup> findings supported by well-designed observational studies showing a dose-dependent decreased presence of reflux symptoms following weight reduction. A large prospective observational study showed reduced reflux symptoms with tobacco smoking cessation in normal weight individuals.<sup>48</sup> RCTs also showed that early evening meals<sup>49</sup> and head of the bed elevation<sup>52</sup> decreased the esophageal acid exposure time, and dietary fiber decreased reflux symptoms.<sup>50</sup>

Based on the present review, we believe that the evidence of lifestyle modifications in GERD has been strengthened compared to the statements in the four current treatment guidelines.<sup>24,25,34-36</sup> The CAG guideline concludes that lifestyle modifications are ineffective for frequent or severe reflux symptoms and that data are insufficient to support lifestyle modifications in mild reflux.<sup>24</sup> The ACG guideline states that lifestyle modification may benefit some GERD patients, but that such modifications alone are unlikely to control symptoms in the majority of GERD patients.<sup>25</sup> The AGA guideline recommends weight loss in obese GERD patients and elevation of the head of the bed in patients experiencing reflux symptoms when recumbent, while other lifestyle modifications should be individually tailored.<sup>34,35</sup> The guideline by Katz et al. supports avoidance of meals two to three hours before bedtime, in addition to weight loss and head of bed elevation. However, it does not recommend elimination of food that can trigger reflux.<sup>36</sup>

We believe that patients suffering from GERD should be recommended to lose weight if they are obese, that tobacco smoking cessation and increased dietary fiber should be encouraged and that

late evening meals should be avoided and head of the bed elevation recommended for patients with supine reflux. Lifestyle interventions, especially weight loss and tobacco smoking cessation, are also beneficial from other perspectives, including low economic costs, no harmful side-effects and overall health benefits.

As only small RCTs or observational studies of lifestyle intervention have been performed, larger RCTs should be conducted to verify these results. Nevertheless, the available evidence is reasonably consistent and supported by the pathophysiology and epidemiology. The effects of these interventions on reflux symptoms, acid exposure and endoscopic findings should be assessed in future studies. As obesity and smoking are risk factors of GERD, reduced prevalence of these exposures in the populations could also reduce the incidence of GERD.

## CONCLUSIONS

Recent evidence supports lifestyle intervention in the treatment of GERD. These include weight loss, tobacco smoking cessation, dietary interventions and head of the bed elevation. Meanwhile, the awareness of adverse effects of medical treatment has increased, questioning long-term and continuous PPI therapy, at least in mild GERD.

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## FIGURE LEGEND

**Figure. Flowchart of literature search**

## TABLE

**Table. Lifestyle intervention in gastroesophageal reflux disease (GERD)**

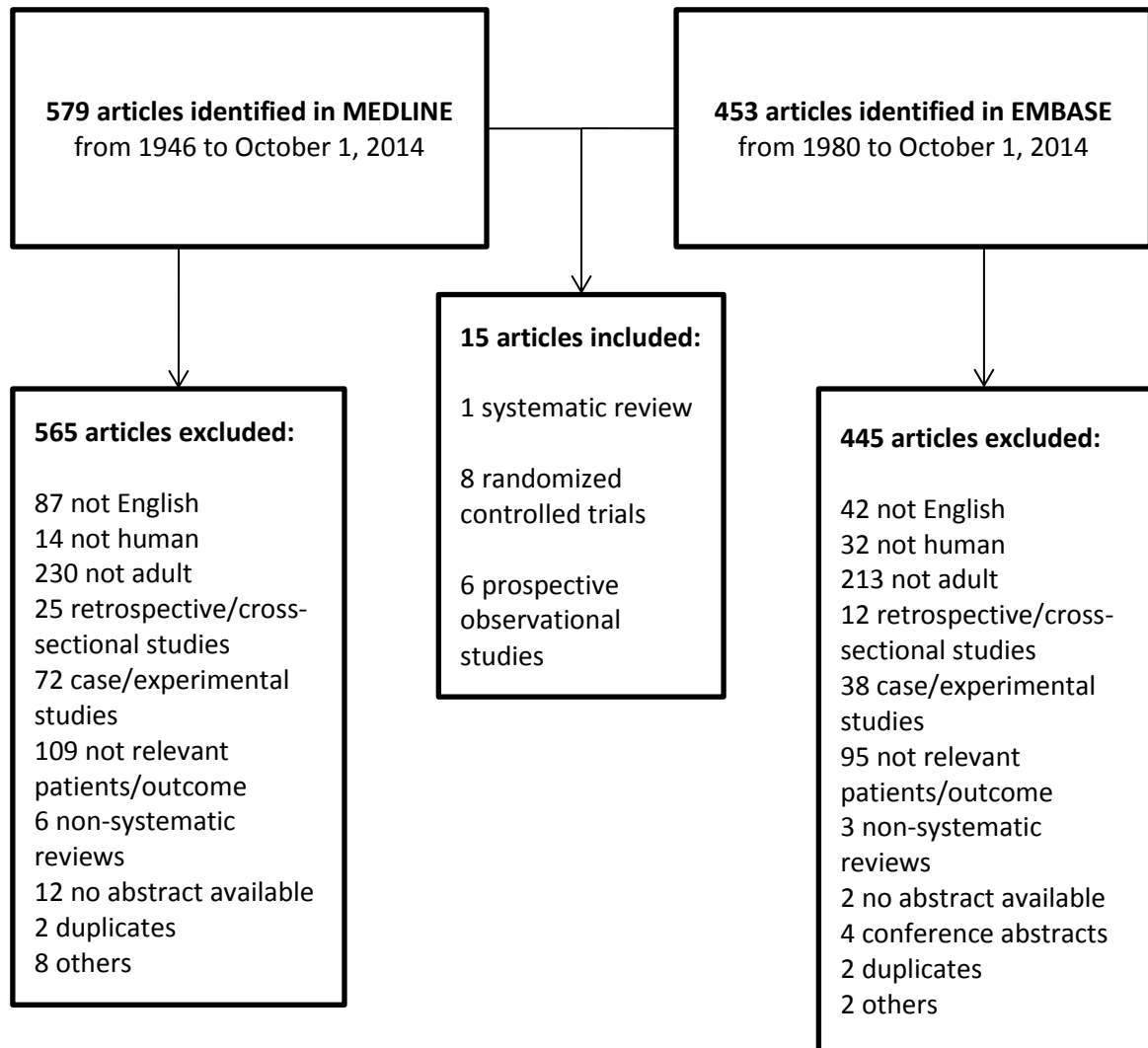
Category	Study	Design	Intervention	Findings	Level of evidence <sup>a</sup>	Comparison with current guidelines			
						CAG <sup>b</sup>	ACG <sup>c</sup>	AGA <sup>d</sup>	Katz et al.
Weight loss	Mathus-Vliegen et al. 1996	RCT <sup>e</sup>	Gastric balloon vs. sham treatment	Normalization of pH-measurements in 3 of 5 with weight loss	A	Lifestyle modifications are ineffective for frequent or severe symptoms, but may be beneficial if obvious dietary precipitants, obesity or tobacco smoking	Lifestyle modifications may benefit many GERD patients, but are unlikely to control symptoms in the majority	Weight loss in obese patients, head of the bed elevation if symptoms when recumbent and other lifestyle modifications tailored to the individual patient	Weight loss recommended for GERD patients with overweight or recent weight gain; Head of bed elevation and avoidance of meals 2 – 3 hour before bedtime recommended if nocturnal GERD; Routine global elimination of food that can trigger reflux not recommended
	Mathus-Vliegen et al. 2002	RCT <sup>e</sup>	Gastric balloon vs. sham treatment	Reduced acid exposure in sham group (the effect of mere weight loss)					
	Mathus-Vliegen et al. 2003	RCT <sup>e</sup>	Gastric balloon vs. sham treatment	Reduced acid exposure in sham group (the effect of mere weight loss)					
	Singh et al. 2013	RCT <sup>e</sup>	Structured weight loss program vs. telephone-based group conference	Decreased symptom prevalence and score in both groups					
	Austin et al. 2006	Non-randomized prospective study	Very low-carbohydrate diet	Decreased acid exposure and symptom score					
	Fraser-Moodie et al. 1999	Non-randomized prospective study	Dietary advice	Decreased symptom score					
	Jacobson et al. 2006	Prospective population-based cohort study	No intervention	Dose-dependent decrease in symptom prevalence					

	Ness-Jensen et al. 2013	Prospective population-based cohort study	No intervention	Dose-dependent decrease in symptoms, improved medical treatment success					
	Cremonini et al. 2006	Prospective population-based cohort study	No intervention	No association with symptoms					
	Kjellin et al. 1996	RCT <sup>e</sup>	Low-caloric diet vs. control	No effect on symptoms, endoscopic findings or acid exposure					
<b>Tobacco smoking cessation</b>	Ness-Jensen et al. 2013	Prospective population-based cohort study	No intervention	Decreased symptoms in normal weight individuals	B				
<b>Dietary interventions</b>	Kjellin et al. 1996	RCT <sup>e</sup>	<b>Low-caloric diet vs. control</b>	No effect on symptoms, endoscopic findings or acid exposure	B (no effect)				
	Austin et al. 2006	Non-randomized prospective study	<b>Very low-carbohydrate diet</b>	Decreased acid exposure and symptom score	B				
	Piesman et al. 2007	RCT <sup>e</sup>	<b>Late vs. early evening meal</b>	Decreased acid exposure with early evening meal	B				
	DiSilvestro et al. 2011	RCT <sup>e</sup>	<b>Dietary fiber vs. placebo</b>	Decreased symptom prevalence and score with dietary fiber	B				
	Johnson et al. 2010	Systematic review of observational	<b>Carbonated beverages</b>	No effect on GERD	B (no effect)				

studies

<b>Head of the bed elevation</b>	Hamilton et al. 1988	RCT <sup>e</sup>	Head of bed elevation vs. flat position	Decreased acid exposure with head of bed elevation	B				

<sup>a</sup> **A** - Multiple populations evaluated, data derived from multiple randomized clinical trials or meta-analyses; **B** - Limited populations evaluated, data derived from a single randomized clinical trial or non-randomized studies; **C** - Very limited populations evaluated, only consensus opinion of experts, case studies or standard of care. <sup>b</sup> Canadian Association of Gastroenterology. <sup>c</sup> American College of Gastroenterology. <sup>d</sup> American Gastroenterological Association. <sup>e</sup> Randomized clinical trial.



eTable. Summary of literature search

Source	Search terms	Id. articles	Incl	Meta-analysis	Systematic review	Randomized clinical trial	Prospective observational study	Excl	Not English	Not human	Not adult	Retrospect /cross-sect study	Case/ experim study	Not relevant patients/ outcome	Non-systematic review	No abst available	Conf abstract	Dupl	Other
MEDLINE/ PubMed <sup>a</sup> 1946 - Oct 1, 2014	"Body Weight Changes"[Mesh]	201	8				4	4	141	21	3	88	1	4	23		1		
							Singh et al. 2013 Kjellin et al. 1996 Mathus-Vliegen et al. 2002 Mathus-Vliegen et al. 2003	Ness-Jensen et al. 2013 Cremonini et al. 2006 Jacobson et al. 2006 Fraser-Moodie et al. 1999											
	Excluding obesity surgery	-52	0					0											
	"Smoking Cessation" [Mesh]	12	1				1	11	3		4	1	1	2					
							Ness-Jensen et al. 2013												
	"Diet Therapy"[Mesh]	72	1				1	71	22	4	27	1	1	9	2	3		2	
							(Kjellin et al. 1996)	Austin et al. 2006 (Fraser-Moodie et al. 1999)											
	"Meals"[Mesh]	6	0					6	1		2								3

eTable. Continued

[illegible]



eTable. Continued

Source	Search terms	Id. articles	Incl	Meta-analysis	Systematic review	Randomized clinical trial	Prospective observational study	Excl	Not English	Not human	Not adult	Retrospect /cross-sect study	Case/ experim study	Not relevant patients/ outcome	Non-systematic review	No abst available	Conf abstract	Dupl	Other
	"Posture"[Mesh] c	73	2			2		71	6		28	1	8	28					
						Piesman et al. 2007 Hamilton et al. 1988													
	"Exercise" [Mesh]	54	0					54	4		12	10	21	6	1				
	Sum	579	14	0	1	7	6	565	87	14	230	25	72	109	6	12	0	2	8

eTable. Continued

Source	Search terms	Id. articles	Incl	Meta-analysis	Systematic review	Randomized clinical trial	Prospective observational study	Excl	Not English	Not human	Not adult	Retrospect /cross-sect study	Case/ experim study	Not relevant patients/ outcome	Non-systematic review	No abst available	Conf abstract	Dupl	Other
EMBASE/ OvidSP <sup>b</sup> 1980 - Oct 1, 2014	weight reduction	104	6			4	2	73	3	6	35		1	27			1		
						Singh et al. 2013 Mathus-Vliegen et al. 1996 Mathus-Vliegen et al. 2002 Mathus-Vliegen et al. 2003	Ness-Jensen et al. 2013 Fraser-Moodie et al. 1999												
	excluding obesity surgery	-25	0					0											
	smoking cessation	65	1				1	64	2	0	42		1	17			2		
							Ness-Jensen et al. 2013												
	diet therapy	38	1				1	37	5	5	22			5					
							Austin et al. 2006												
	diet	51	0					51	10	6	21	3	1	10					
	meals	11	0					11	2		4		2	3					

eTable. Continued

Source	Search terms	Id. articles	Incl	Meta-analysis	Systematic review	Randomized clinical trial	Prospective observational study	Excl	Not English	Not human	Not adult	Retrospect /cross-sect study	Case/ experim study	Not relevant patients/ outcome	Non-systematic review	No abst available	Conf abstract	Dupl	Other
	<i>fat</i>	6	0					6			2		3	1					
	<i>carbohydrate</i>	6	0					6			3		2				1		
	<i>cacao</i>	2	0					2					1	1					
	<i>mentha piperita</i>	1	0					1							1				
	<i>coffee</i>	14	0					14	1		7	1	1	4					
	<i>alcohol</i>	44	0					44	11	4	16	1	2	7	1				2
	<i>citrus</i>	0	0					0											
	<i>carbonated beverages</i>	10	0					10		1	5		3	1					
	<i>spices</i>	1	0					1						1					
	<i>dietary fiber</i>	21	0					21			9	1	2	7		1		1	
	<i>posture</i>	47	0					47	5	8	23	1	6	3		1			
	<i>exercise OR physical activity</i>	57	0					57	3	2	24	5	13	8	1			1	
	<b>Sum</b>	453	8	0	0	4	4	445	42	32	213	12	38	95	3	2	4	2	2

<sup>a</sup>MeSH terms (exploded, including all subheadings): ("Gastroesophageal Reflux"[Mesh] OR "Heartburn"[Mesh] OR "Esophagitis, Peptic"[Mesh]) AND (...)

<sup>b</sup>EMTREE terms (exploded outcome, focused intervention, including all subheadings): (gastroesophageal reflux OR heartburn OR non erosive reflux disease OR reflux esophagitis) AND (...)

<sup>c</sup>Search limited to meta-analysis, systematic review, clinical trial and observational study

